REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 79 and 80 have been amended. Claims 79-97 and 110-115 are in the case and are before the Examiner.

I. The Amendments

Claims 79 and 80 have been amended to recite sequences against which one can compare a sequence for ascertaining the percentage of substitution. Support for this amendment can be found at least at page 47 of the specification or Paragraphs [0152-0153] of the published application No. 20040152876.

Each of the claims has also been amended to remove the previously added conditions in favor of a more expansive recitation of the conditions under which the chimer particles' protein enhanced stability is measured. This stability is directed at the proteins themselves as is seen from the SDS-PAGE gel results shown in Figs. 3, 4 and 8. Specific support for those recitations can be seen from those figures and least from paragraphs [0092], [0348-0357], Examples 6, 7, 22 and 23, Paragraphs [0469-0475, and 0476-0482] of the published specification (20040156864).

It is thus seen that no new matter has been added.

II. The Action

Rejection Under 35 USC §112, First Paragraph

The added phrase complained of in Paragraphs 17-18 of the present Action is shown by the underlining below

> being more stable on storage at 1 mg/mL using 50 mM $NaPO_4$, pH 6.8 than are particles formed from an otherwise identical HBc chimer molecule that lacks said C-terminal cysteine residue or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue

has been cancelled to speed prosecution. However, it is noted that the phrase is well supported in the specification as was stated in the prior reply. That deleted phrase has been replaced by a further recitation concerning the manner in which the stability of the protein that constitutes the immunogenic particles is assayed, and that language is also well supported as is discussed above.

It is well settled that claim language need not be present *ipsis verbis* or *in heac verba* in the specification for claim language to be supported. See, *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). The purpose of the "WRITTEN DESCRIPTION" section of 35 USC §112 was said in *Vas-Cath* to convey "with reasonable clarity to those skilled in the art that, as of the filing date sought, [the inventor] was in possession of the invention." See, also MPEP section 2163.02 third paragraph, first sentence.

The Action has also cited *In re Rasmussen*. That citation is inapt for several reasons. First, the citation is incorrect. It should be 211 USPQ 325, not 210 USPQ 325.

Second, and more importantly, *Rasmussen* discussed a broadening amendment. The amendments complained of here are narrowing amendments.

Third, and more important still, the Court found in favor of the applicant and held that even though he did not have *ipsis verbis* support, the specification's disclosure supported the proposed amendments. The same support should be found here.

B. Rejections Under 35 USC §103(a)

(1) Ireland In View of Zlotnick

(2) Zlotnick in view of Pumpens

(3) Thornton in view of Zlotnick

All of the presently pending claims were rejected as allegedly obvious from one or more of the above combinations of teachings. Each of these rejections suffers from the same hindsight reconstruction fault, and is respectfully traversed.

As held and recited by the CCPA,

> "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." [*In re Wesslau*, 147 USPQ 391, 393 (CCPA 1965); see also *In re Mercer*, 185 USPQ 774, 778 (CCPA 1975).]

It is again submitted that the Action has done just that, picked and chosen only so much as would support a given position and then excluded those parts of the relied-on disclosures that did not fit its preconceived notions. Because of the commonality of error in the bases for rejection, the rejections will be dealt with together after a brief review of the teachings of each document.

The Action began by requiring a completely new entity to be formed, and as such, has set an impossible burden to overcome to find non-obviousness. Following the logic of this Action, only the invention of new elements as was done when Elements 95 and 96 were claimed by the late Glenn T. Seaborg in US Patents No. 3,156,523 and No. 3,161,462, respectively, would be sufficiently free of pre-existing elements to gain patentability. It is submitted that even after the *KSR* decision, a holding of obviousness requires more.

Ireland taught insertion of a peptide sequence from the inhibin molecule into the HBc molecule at the C-terminal position of a truncated HBc whose C-terminal final HBc residue is residue 144, and also within the sequence of the full-length core polypeptide at position 78. Thus, the former chimer contained no C-terminal Cys, whereas the latter contained a Cys at position 183 or 185, depending on which strain of HBV was used. Neither insertion nor resulting chimer is useful in leading to the claimed invention.

The Action noted that all of the claims recite that the substitutions present are conservative. It is again submitted that an Ala for Cys substitution taught by Zlotnick is not "conservative", and that being the case, the Zlotnick

teaching is not properly combinable with any other relied-on disclosure.

Thus, when combined with Ireland, one must C-terminally truncate the construct used by Ireland and if one put Ireland's peptide into Zlotnick's Cp*150 construct there would be non-conservative substitutions at positions 48, 61 and 107. A similar result occurs when the Pumpens and Zlotnick teachings are combined. When one studies Thornton, one finds that the inserted sequence can be placed almost anywhere in the HBc sequence. It is submitted that that disclosure is so diffuse as to be of no use to any worker without undue experimentation as to what would work and form particles. Even if one were to combine the teachings of Thornton and Zlotnick, the same result would occur as happened with the combinations of Zlotnick and either Pumpens or Ireland; i.e., a construct not within those encompassed by the claims.

Examined somewhat differently, (i) HBc proteins that contained added non-HBc sequences but were unstable on storage existed in the art. It was also known from Zlotnick that (ii) elimination of all internal cysteine residues from a C-terminal truncated HBc protein plus the addition of a single heterologous residue at the C-terminus produced particles that could better withstand being in a 3.5 M urea denaturing solution than could particles produced from a similar disulfide-reduced protein or a cysteine-free protein. The reported result from that dunking of particles in denaturant for an unspecified time was that the particles containing the C-terminal cysteine stayed together, whereas those without any cysteines were denatured, dissociated and formed two peaks in the size exclusion study shown in Zlotnick's Fig. 2b. The results shown in Fig. 2a indicate that

the protein of the cysteine-containing chimers polymerized at pH 9.5 were less pure than that polymerized at pH 7.5.

It is respectfully submitted that Zlotnick is, at worst, silent on the issue of protein stability of chimers with and without cysteines. Indeed, it is rather urged from the extra band seen in the monomer region of lane 7 of Zlotnick's Fig. 2a that having the added cysteine caused a protein stability problem with those chimers. Thus, there were two or possibly three protein bands in lane 7 for the cysteine-containing chimer, with only one band being seen for any of the cysteine-free proteins.

It is thus submitted that Zlotnick has no positive teaching related to particle stability in the form of preventing protein degradation, as compared to particle dissociation stability. The claims have been amended to clarify that the stability recited relates to the proteins of the particles. That is what the underlying stability data show. Copies of Figs. 3, 4, and 8 are attached to this paper for the Examiner's convenience.

The enhanced stability claimed here does not relate to the equilibrium of monomeric (or dimeric) and polymeric forms in the particles themselves as is disclosed by Zlotnick. As such, it is of little moment to the present invention whether "disulfide bond formation by Cp*150 can promote capsid assembly" because capsid assembly does not equate to nor suggest protein stability from degradation on dissolution of chimer protein particles in aqueous buffer at 37^{O} C for about two weeks.

The present disclosure and claims are directed to those of ordinary skill in the art. It is submitted that an

ordinarily skilled worker here has a PhD or MD degree, or both, several years of experience as a leader of a research group of several advanced degreed workers, and has published several papers relating to HBc chimers as a sole or lead author.

It is reiterated that the previously cited and discussed paper by Ulrich, a worker of at least ordinary skill if not extraordinary skill, that stated that the stability problem of HBc was not solved prior to the application's filing date is particularly relevant here. That that is the case is illustrated by the fact that Ulrich had published at least 24 papers since 2002 in viral-related technologies. He was a lead author in this field for years before and after the relied-on publications by Pumpens and Zlotnick. He has published papers co-authored with Pumpens as will be seen in the attached Exhibits that are discussed hereinafter. "It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case, patent cases included." *Stratoflex Inc. v. Aeroquip Corp.*, 218 USPQ 871, 879 (Fed. Cir. 1983).

The Examiner's attention is again invited to *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579; 27 USPQ2d 1200 (1993). The Court noted that the "fact of publication (or lack thereof) in a peer reviewed journal thus will be a relevant, though not dispositive, consideration in assessing the scientific validity of a particular technique or methodology on which an opinion is based." (27 USPQ2d at 1206.)

It is again submitted that Ulrich's writings should be afforded more weight than the unsupported suppositions as to what may be in the mind of a hypothetical person of ordinary skill. Rather, Ulrich is (was) an author of probably greater

than ordinary skill. Ulrich wrote in a peer-reviewed paper published after both relied-on documents and before the filing of the instant application's earliest parent application that a problem of chimer usage in vaccines related to the requirement of reproducible preparation of intact chimer particles that were stable and could withstand long-term storage.

Ulrich did not put together the combination of the two teachings to solve the stability problem that he wrote about, but rather maintained that the problem still had to be solved. Ulrich, Pumpens and other authors published enclosed Exhibit I [Lachmann et al., *Intervirology* 1999; **42**:51-56] about a year prior to the filing of the earliest parental application here and cited the relied-on Zlotnick paper as note [16]. Counsel has found a single reference to [16] and that is on page 55. The point for which Zlotnick was cited is the following:

> Similarly, C-terminal fusions [of inserted peptide sequences] were found again to be lower immunogenic [sic] than c/e1 insertions [8]. These data are in line with structural data suggesting a luminal localization of the C-terminal region [16].

It is submitted that if Ulrich the real, live worker of more than ordinary skill working and writing in this art did not put together the relied-on art as has the hypothetical skilled worker of the Action, the Action is mistaken in its conclusion as to the abilities of its hypothetical worker and obviousness, and that conclusion of obviousness should be withdrawn.

In another published paper entitled "Stability and Morphology Comparisons of Self-Assembled Virus-Like Particles

from Wild-Type and Mutant Human Hepatitis B Virus Capsid Proteins" Newman et al., *J. Virol.*, Dec. 2003; **77(24)**:12950-12960, (enclosed Exhibit II), the authors cited the Zlotnick paper at page 12959 as note (39) for

> [u]sing spectrophotometric measurement, Zlotnick et al. estimated the stoichiometry of encapsidated RNA and *E. coli*-derived capsid particles to be near a total of 3,000 ribonucleotides per full-length capsid particle (95% T=4) (39).

The Abstract of that paper states in part:

> [w]e found no significant differences in capsid stability between wild-type and mutant I97L particles [those whose isoleucine at position 97 was mutated to a leucine] under denaturing pH and temperature in either full-length or truncated core protein contexts. In general, HBV capsid particles (HBcAg1-183, HBcAg1-149, and HBcAg1-140) are very robust but will dissociate at pH 2 or 14, at temperatures higher than 75^{o}C, or in 0.1% sodium docecyl sulfate (SDS).

The lead (corresponding) author of Newman et al. is Dr. Chiao Shih, a full Professor in the Departments of Pathology and of Microbiology and Immunology at the University of Texas Medical Branch. Examination of his profile, which was obtained from the University web site and is attached as Exhibit III, shows that he as been the lead author of several peer-reviewed articles dealing with hepatitis B core. It must be agreed that the Newman et al. paper is concerned with particle stability from its title and the second quote above. Thus, from the above quotes, we have another worker of more than ordinary skill in the art who cited the Zlotnick paper, but failed to make the

connection that is asserted to be obvious to a worker of lesser skill; i.e., ordinary skill.

The Examiner's attention is again invited to the paper by Zhou and Standring that was cited in the prior Action. That paper, Zhou et al., *J. Virol.* **66(9):**5393-5398 (Sept 1992; hereinafter Zhou), discussed results obtained with full length HBc whose four native Cys residues were exchanged for Ala residues, as well as similarly Ala-for-Cys mutated C-terminal-truncated constructs ending with residues 149 and also 172. That paper reported that

> Cys residues and disulfides are not required for the assembly of either HBV capsids or the dimers that provide the precursors for capsid assembly. . . . Cys residues stabilize isolated p21.5 structures, as evidenced by the marked reduction in stability of Cys-minus dimers and capsids . . . (Abstract)

The Zhou paper thus is substantially similar in its disclosures to the disclosures of Zlotnick in regard to the effect of the Cys residues on stability of particular constructs, although Zlotnick did not cite the Zhou paper. The relied-on Pumpens paper cited Zhou as did the above Ulrich paper. The Zhou and Zlotnick papers were also cited in an otherwise redundant review by Pumpens and Grens, *FEBS Letters*, **442**:1-6 (1999), that was provided previously.

Notwithstanding the fact that skilled workers Pumpens and Ulrich not only knew of the Zhou and Zlotnick papers, but cited them, neither group of skilled worker authors put together the earlier Pumpens paper with either of those disclosures to

solve the problem of stability as has the present inventor. Here were workers of at least ordinary skill in this art, if not greater than ordinary skill, and they did not do what the Action has asserted would have been obvious to a mere worker of ordinary skill. It is again submitted that the claimed subject matter was not obvious to a worker of ordinary skill in the art as of its filing date, and this rejection should be withdrawn.

III. Additional Information That May Be Material

In view of the holding in *McKesson Information Solutions, Inv. V. Bridge Medical, Inc.* (Fed. Cir. May 18, 2007; 06-1517), enclosed herewith are copies of Actions from an application relating to recombinant hepatitis B core particles and their use that might be deemed material to the prosecution of the present application. It is noted that the Examiner handling this application is also handling divisional applications Serial No. 10/805,913 and Serial No. 10/806,006, as well as applications Serial No. 10/732,862 and Serial No 10/787,734 so the Actions from those applications are not being included herewith. The enclosed Actions are from Application Serial No. 10/677,074, and are noted on enclosed Form PTO/SB/08B.

IV. Summary

Claims 79 and 80 have been amended. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

A fee for the filing of the Actions from the other application is enclosed. No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By _____
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Enclosures
- Exhibits I-III.
- Petition and Fee
- IDS Fee for filing Actions
- Actions from other application, Form PTO/SB/08B
- Figs. 3, 4, and 8